PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5181-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/36977	International filing date *(day/month/year)* 04 November 2004 (04.11.2004)	Priority date *(day/month/year)* 04 November 2003 (04.11.2003)
International Patent Classification (IPC) or national classification and IPC		
IPC: **G01N 33/48**(2006.01),**33/574**(2006.01) USPC: 435/4,7.1,7.23,40.5;436/64,500		
Applicant		
BAYER PHARMACEUTICALS CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 May 2005 (25.05.2005)	01 February 2007 (01.02.2007)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Karen A. Canella Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/36977

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-20 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☒ the claims:
pages 21-24 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☒ the drawings:
pages 1 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/36977

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-6, 15-25	YES
	Claims 7-14	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-25	NO
Industrial Applicability (IA)	Claims 1-25	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)
Please See Continuation Sheet

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:

V. 2. Citations and Explanations:

Claims 7-14 lack novelty under PCT Article 33(2) as being anticipated by JERGENSEN et al

Claim 7 is drawn to a method for providing a patient diagnosis for cancer, comprising the steps of : (a) determining the level of expression of one or more proteins in a first biological sample taken from the patient; (b) determining the level of expression of one or more proteins in at least a second biological sample taken from a normal patient sample; and (c) comparing the level of expression of one or more proteins in the first biological sample with the level of expression of one or more proteins in the second biological sample; wherein a change in the level of expression of one or more proteins in the first biological sample compared to the level of expression of one or more proteins in the second biological sample is a diagnostic of the disease. Claim 8 embodies the method of claim 7, wherein said protein is pERK. Claim 9 embodies the method of claim 7, wherein said cancer is selected from lung cancer, renal cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, thyroid cancer, ovarian cancer, breast cancer, prostate cancer, and melanoma. Claim 10 embodies the method of claim 7, wherein the protein expression level is assessed by immunohistochemistry. Claim 11 embodies the method of claim 7, wherein said sample is a tumor biopsy.

Claim12 is drawn to a method for distinguishing between normal and disease tissues, comprising the steps of : (a) determining the level of expression of one or more proteins in a first biological sample of a disease tissue; (b) determining the level of expression of one or more proteins in at least a second biological sample taken from normal tissue; and (c) comparing the level of expression of one or more proteins in the first biological sample with the level of expression of one or more proteins in the second biological sample; wherein a change in the level of expression of one or more proteins in the first biological sample compared to the level of expression of one or more proteins in the second biological sample is indicative of a disease state.

Claim 13 embodies the method of claim 12, wherein said protein is pERK. Claim 14 embodies the method of claim 12, wherein the protein expression level is assessed by immunohistochemistry.

JERGENSEN et al disclose a method wherein samples of tumor biopsy material comprising primary malignant melanoma is differentiated from metastatic melanoma and begnin nevi on the basis of immunohistochemical analysis of phosphorylated Erk.

Supplemental Box

Claims 7-14 lack novelty under PCT Article 33(2) as being anticipated by ADEYINKA et al.

ADEYINKA et al disclose a method wherein human primary tumor breast biopsy samples and metastatic breast lesions are detected by means of polyclonal antibody which binds to activated MAPK which will stain phosphorylated Erk.

Claims 1, 3, 4, 15, 16, 18, 19, 21 and 22 lack an inventive step under PCT Article 33(3) as being obvious over TANIMURA et al.

Claim 1 is drawn to a method to monitor the response of a patient being treated for cancer by administering an anti-cancer agent, comprising the steps of : (a) determining the level of expression of one or more proteins in a first biological sample taken from the patient prior to treatment with the anti-cancer agent; (b) determining the level of expression of one or more proteins in at least a second biological sample taken from the patient subsequent to the treatment with the anti- cancer agent; and (c) comparing the level of expression of one or more proteins in the second biological sample with the level of expression of one or more proteins in the first biological sample; wherein a change in the level of expression of one or more proteins in the second biological sample compared to the level of expression of one or more proteins in the first biological sample indicates the efficacy of the treatment with the anti-cancer agent. Claim 3 embodies the method of claim 1, wherein said protein is pERK. Claim 4 embodies the method of claim 1, wherein said cancer is selected from lung cancer, renal cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, thyroid cancer, ovarian cancer, breast cancer, prostate cancer, and melanoma.

Claim 15 is drawn to a method for discovering novel drugs for the treatment of cancer, comprising the steps of : (a) determining the level of expression of one or more proteins in a first tumor cell sample prior to treatment with the anti-cancer agent; (b) determining the level of expression of one or more proteins in at least a second tumor cell sample subsequent to the treatment with the anti-cancer agent; and (c) comparing the level of expression of one or more proteins in the second tumor cell sample with the level of expression of one or more proteins in the first tumor cell sample; wherein a change in the level of expression of one or more proteins in the second tumor cell sample compared to the level of expression of one or more proteins in the first tumor cell sample indicates the efficacy of the anti-cancer agent. Claim 16 embodies the method of claim 15, wherein said protein is pERK. Claim 18 embodies the method of claim 15, wherein said tumor cells are selected from lung cancer, renal cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, thyroid cancer, ovarian cancer, breast cancer, prostate cancer, and melanoma.

Claim 19 is drawn to a method for selecting patients eligible for anti-cancer treatment, comprising the steps of (a) determining the level of expression of one or more proteins in a first biological sample taken from a patient; (b) comparing the level of expression of one or more proteins in the first biological sample with the level of expression of one or more proteins in a second biological sample taken from a normal patient sample; wherein a change in the level of expression of one or more proteins in the first biological sample compared to the level of expression of one or more proteins in the second biological sample is a prognostic of that patient's response to anti-cancer treatment.

Claim 21 embodies the method of claim 19, wherein said protein is pERK. Claim 22 embodies the method of claim 19, wherein the patient has been diagnosed with cancer is selected from lung cancer, renal cancer, pancreatic cancer, liver cancer, gastrointestinal cancer, thyroid cancer, ovarian cancer, breast cancer, prostate cancer, and melanoma.

TANIMURA et al teach that a specific blockade of the Erk pathway is expected to result in anti-metastatic effect in tumor cells and that the ERK pathway is a therapeutic target for development of anti-cancer drugs. Therefore, it would have been prima facie obvious at the time the claimed invention was made to screen candidate drugs by the effect on ERK expression. One of skill in the art would have been motivated to do so by the teachings of TANIMURA regarding the inhibition of the ERK pathway and the suggestion that novel drugs can be identified by their ability to block the ERK pathway.

Claims 19 and 21-24 lack an inventive step under PCT Article 33(3) as being obvious over ADEYINKA et al. in view of TANIMURA et al.

Claim 23 embodies the method of claim 19, wherein the protein expression level is assessed by immunohistochemistry. Claim 24 embodies the method of claim 19, wherein said sample is a tumor biopsy.

ADEYINKA et al teach a method wherein human primary tumor breast biopsy samples and metastatic breast lesions are detected by means of polyclonal antibody which binds to activated MAPK which will stain phosphorylated Erk ADEYINKA et al teach that Activated MAPK Expression is associated with lymph node metastasis.

TANIMURA et al teach that a specific blockade of the Erk pathway is expected to result in anti-metastatic effect in tumor cells and that the ERK pathway is a therapeutic target for development of anti-cancer drugs. Therefore, it would have been prima facie obvious at the time the claimed invention was made to screen candidate drugs by the effect on ERK expression.

It would have been prima facie obvious at the time the claimed invention was made to select patients for anti-ERK chemotherapy by screening for activated ERK in the lymph nodes of breast cancer patients. One of skill in the art would have been motivated to do so by the teachings of TANIMURA et al regarding the expectation that blockade of the ERK pathway would be expected to result in an anti-metastatic effect.

Claims 5, 10, 14, 17, 23 and 25 lack an inventive step under PCT Article 33(3) as being obvious over ADEYINKA et al. in view of TANIMURA et al. as applied to claims 19 and 21-24 above, and in further view of JERGENSEN et al.

Claims 5, 17 and 23 embody the methods of claims 1, 15 and 19, respectively, wherein the protein expression level is assessed by immunohistochemistry. Claim 25 is drawn to a kit comprising a primary antibody directed to pERK, a secondary antibody, reagents, reference samples, and control samples.

ADEYINKA et al teach a method wherein human primary tumor breast biopsy samples and metastatic breast lesions are

Supplemental Box

detected by means of polyclonal antibody which binds to activated MAPK which will stain phosphorylated Erk ADEYINKA et al teach that Activated MAPK Expression is associated with lymph node metastasis.

TANIMURA et al teach that a specific blockade of the Erk pathway is expected to result in anti-metastatic effect in tumor cells and that the ERK pathway is a therapeutic target for development of anti-cancer drugs. Therefore, it would have been prima facie obvious at the time the claimed invention was made to screen candidate drugs by the effect on ERK expression.

It would have been prima facie obvious at the time the claimed invention was made to substitute an specific antibody with binds to phosphorylated Erk for the polyclonal antibody which binds to activated MAPK in the method of ADEYINKA et al. One of skill in the art would have been motivated to do so by the teachings of TANIMURA regarding the significance of the inhibition of the ERK pathway. One of skill in the art would understand that phosphorylated Erk is part of the ERK pathway.

Claims 2 and 20 lack an inventive step under PCT Article 33(3) as being obvious over ADEYINKA et al. in view of TANIMURA et al. as applied to claims 19 and 21-24 above, and in further view of FU et al.

Claims 2 and 20 embody the methods of claims 1 and 19, respectively, wherein said anti-cancer agent is a Raf kinase inhibitor.

ADEYINKA et al teach a method wherein human primary tumor breast biopsy samples and metastatic breast lesions are detected by means of polyclonal antibody which binds to activated MAPK which will stain phosphorylated Erk ADEYINKA et al teach that Activated MAPK Expression is associated with lymph node metastasis.

TANIMURA et al teach that a specific blockade of the Erk pathway is expected to result in anti-metastatic effect in tumor cells and that the ERK pathway is a therapeutic target for development of anti-cancer drugs. Therefore, it would have been prima facie obvious at the time the claimed invention was made to screen candidate drugs by the effect on ERK expression.

Fu et al teach that a specific Raf-kinase inhibitor, RKIP, is a clinically relevant suppressor of metastases. FU et al teach that Raf-kinase unregulated the phosphorylation and activation of Erk and that suppression of Raf-kinase inhibits the activation of Erk and subsequent metastases.

It would have been prima facie obvious at the time he claimed invention was made to use Raf-kinase inhibitors to inhibit the formation of phosphorylated Erk. One of skill in the art would have been motivated to do so by the teachings of FU et al connecting the inhibition of Raf-kinase with the suppression of metastases.

---------- NEW CITATIONS ----------